| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/840,125 | SPLAWSKI ET AL. | |
| | Examiner | Art Unit | |
| | Jehanne Souaya Sitton | 1634 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed 2/3/2004*.

2. ☒ The allowed claim(s) is/are *26-30,34-44 and 50*.

3. ☒ The drawings filed on *24 April 2001* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

## EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Jeffrey Ihnen on 4/20/2004.

The application has been amended as follows:

In claim 27, delete the recitation of "A" in line 1 and insert instead --An isolated --.

Claim 28 (Amended): A method for detecting a mutation in SCN5A said mutation selected from the group consisting of G3340A, C4501G, del4850-4852, G4868T, and G5360A which comprises analyzing a sequence of said SCN5A DNA [gene] or RNA from a human sample or analyzing the sequence of cDNA made from mRNA from said sample, for said mutation.

Claim 29 (Amended): The method of claim 28 wherein said mutation is detected by a method selected from the group consisting of:

a) hybridizing a probe specific for one of said mutations to RNA isolated from said human sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said mutation in the sample;

b) hybridizing a probe specific for one of said mutations to cDNA made from RNA isolated from said sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said mutation in the sample;

c) hybridizing a probe specific for one of said mutations to genomic DNA isolated from said sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said mutation in the sample;

d) amplifying all or part of said [gene] SCN5A DNA in said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids;

e) amplifying part of said [gene] SCN5A DNA in said sample using a primer specific for one of said mutations and detecting the presence of an amplified product, wherein the presence of said product indicates the presence of said mutation in the sample;

f) molecularly cloning all or part of said [gene] SCN5A DNA in said sample to produce a cloned nucleic acid and sequencing the cloned nucleic acid;

g) amplifying said [gene] SCN5A DNA to produce amplified nucleic acids, hybridizing the amplified nucleic acids to a DNA probe specific for one of said mutations and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said mutation;

h) forming single-stranded DNA from a gene fragment of said [gene] SCN5A DNA from said human sample and single-stranded DNA from a corresponding fragment of a wild-type gene, electrophoresing said single-stranded DNAS on a non-denaturing polyacrylamide gel and comparing the mobility of said single-stranded DNAs on said gel to determine if said single-stranded DNA from said sample is shifted relative to wild-type and sequencing said single-

stranded DNA having a shift in mobility;

i) forming a heteroduplex consisting of a first strand of nucleic acid selected from the group consisting of a genomic DNA fragment isolated from said sample, an RNA fragment isolated from said sample and a cDNA fragment made from mRNA from said sample and a second strand of a nucleic acid consisting of a corresponding human wild-type gene fragment, analyzing for the presence of a mismatch in said heteroduplex, and sequencing said first strand of nucleic acid having a mismatch;

j) forming single-stranded DNA from said [gene] SCN5A DNA of said human sample and from a corresponding fragment of an allele specific for one of said mutations, electrophoresing said single-stranded DNAs on a non-denaturing polyacrylamide gel and comparing the mobility of said single-stranded DNAs on said gel to determine if said single-stranded DNA from said sample is shifted relative to said allele, wherein no shift in electrophoretic mobility of the single-stranded DNA relative to the allele indicates the presence of said mutation in said sample; and

k) forming a heteroduplex consisting of a first strand of nucleic acid selected from the group consisting of a genomic DNA fragment of said [gene] SCN5A DNA isolated from said sample, an RNA fragment isolated from said sample and a cDNA fragment made from mRNA from said sample and a second strand of a nucleic acid consisting of a corresponding gene allele fragment specific for one of said mutations and analyzing for the presence of a mismatch in said heteroduplex, wherein no mismatch indicates the presence of said mutation.

Claim 35 (Amended): The method of claim 34 wherein said expression product is selected from mRNA of said SCN5A DNA [gene] or a polypeptide encoded by said SCN5A DNA [gene].

Claim 36 (amended): The method of claim 35 wherein one or more of the following procedures is carried out:

(a) observing shifts in electrophoretic mobility of single-stranded DNA from said sample on non-denaturing polyacrylamide gels;

(b) hybridizing a probe to genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene;

(c) determining hybridization of an allele-specific probe to genomic DNA from said sample;

(d) amplifying all or part of said [gene] SCN5A DNA from said sample to produce an amplified sequence and sequencing the amplified sequence;

(e) determining by nucleic acid amplification the presence of a specific mutant allele in said sample,

(f) molecularly cloning all or part of said SCN5A [gene] from said sample to produce a cloned sequence and sequencing the cloned sequence;

(g) determining whether there is a mismatch between molecules (1) said SCN5A DNA [gene genomic DNA] or mRNA isolated from said sample, and (2) a nucleic acid probe complementary to the human wild-type gene DNA, when molecules (1) and (2) are hybridized to each other to form a duplex;

(h) amplification of said SCN5A DNA [gene] sequence[s] in said sample and hybridization of the amplified sequence[s] to nucleic acid probes which comprise wild-type gene sequences,

(i) amplification of said SCN5A DNA [gene] sequence[s] in said tissue and hybridization of the amplified sequence[s] to nucleic acid probes which comprise [said] mutant gene sequences,

(j) screening for a deletion mutation;

(k) screening for a point mutation;

(1) screening for an insertion mutation;

(m) determining *in situ* hybridization of said [gene] SCN5A DNA in said sample with one or more nucleic acid probes which comprise said [gene] SCN5A DNA sequence or a mutant sequence of said [gene] SCN5A;

(n) immunoblotting;

(0) immunocytochemistry;

(p) assaying for binding interactions between said [gene] protein isolated from said tissue and a binding partner capable of specifically binding the polypeptide expression product of a mutant allele and/or a binding partner for the polypeptide[;] and

[(q) ]assaying for the inhibition of biochemical activity of said binding partner.

Claim 37 (Amended): [A] An isolated nucleic acid probe which hybridizes to the isolated DNA of claim 26 under conditions at which it will not hybridize to wild-type SCN5A DNA.

Claim 38 (Amended): A method for diagnosing a mutation which causes long QT syndrome comprising hybridizing a probe which hybridizes [of claim 37] to isolated DNA comprising a sequence of SEQ ID NO: 3 as altered by one or more mutations selected from the group consisting of G3340A, C4501G, del4850-4852, G4868T, and G5360A and not to wildtype SCN5A DNA, to a patient's sample of DNA or RNA, the presence of a hybridization signal being indicative of long QT syndrome.

Claim 39 (Amended): The method according to claim 38 wherein the patient's DNA or RNA has been amplified and said amplified DNA or RNA is hybridized with [a] said probe [of claim 37].

**REASONS FOR ALLOWANCE**

2. The following is an examiner's statement of reasons for allowance: The claims are drawn to isolated nucleic acids comprising SEQ ID NO: 3 as altered by one or more mutation selected from the group consisting of G3340A, C4501G, del4850-4852, G4868T, and G5360A, proteins encoded by said nucleic acids, and methods of detecting such mutations in diagnosing long QT syndrome. The specification teaches that SCN5A DNA is SEQ ID NO: 3 (see page 15). The claims are allowable over the prior art because the prior art does not teach or fairly suggest the mutations in wild-type SCN5A (SEQ ID NO: 3) as set forth in the claims, peptides encoded by such nucleic acids or an association between said mutations and long QT syndrome.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Jehanne Sitton
Primary Examiner
Art Unit 1634
4/26/04